Disease Activity in Rheumatoid Arthritis Patients Stratified by Hemoglobin Levels: A Multi-Center Study

Maryam Salah Al-Mazedi[1], Rajesh Rajan[2*], Adeeba Al-Herz[3], Ahmad Alsaber[4], Mohammed Al-Jarallah[2], Raja Dashti[2], Parul Setiya[5], Khulood Saleh[6], Adel Al-Awadhi[7], Waleed Al-Kandari[6], Eman Hasan[3], Khaled Mokaddem[3], Aqeel Ghanem[8], Ahmad Alenizi[9], Kobalava D. Zhanna[10] and Laura Al Obaid[11]

[1]Department of Medical Laboratory Technology, Public Authority for Applied Education and Training, Kuwait

[2]Department of Cardiology, Sabah Al Ahmed Cardiac Centre, Al Amiri Hospital, Kuwait City, Kuwait

[3]Department of Rheumatology, Al Amiri Hospital, Kuwait City, Kuwait

[4]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, G1 1XH, UK

[5]Department of Agrometeorology, College of Agriculture, G.B.Pant University of Agriculture & Technology, Pantnagar, Uttarakhand, India

[6]Al-Farwaniya Hospital, Sabah Al-Nasser, Farwaniya Governorate, Kuwait

[7]Department of Medicine, Faculty of Medicine, Kuwait University, Jamal Abdul Nasser St, Kuwait City, Kuwait

[8]Mubarak Al-Kabeer Hospital, Jabriya, Hawalli Governorate, Kuwait

[9]Al-Jahra Hospital, Al Jahra, Jahra Governorate, Kuwait

[10]Department of Internal Medicine with the Subspecialty of Cardiology and Functional Diagnostics Named after V.S. Moiseev, Institute of Medicine, Peoples' Friendship University of Russia (RUDN University), Moscow, Russian Federation

[11]Department of Medicine, Faculty of Medicine, Royal College of Surgeons, Dublin, Ireland

Received: 18 September 2023

Accepted: 6 June 2024

*****Corresponding author: cardiology08@gmail.com

DOI 10.5001/omj.2024.101

Abstract

Objectives: Haemoglobin (Hb) levels and its relation to rheumatoid arthritis (RA) is multifactorial. The primary objective of this study was to examine the association between Hb levels and disease activity in patients with RA.

Methods: This retrospective study obtained data from adult RA patients with Hb reports from the Kuwait Registry for Rheumatic Diseases (KRRD). Patients were recruited from four public hospitals in Kuwait between February 2013 and February 2022. The cohort was stratified into two groups: Hb ≤ 110 g/L and Hb > 110 g/L. Demographic, treatment, clinical, and laboratory characteristics were used to compare the two Hb cohorts. Multivariate and univariate statistical analyses were used to analyse the data.

Results: The total number of patients visited (N_v) was 11393 and consecutive patients with RA diagnoses and Hb data (N_p) was 1584. Both N_v and N_p were included in the study. Of these, 72.5% (n = 8260) had high Hb levels and 27.5% had low Hb levels (n = 3133). The average age of the cohort was 55.9±12.5 years. Logistic regression analysis revealed that a greater number of non-Kuwaiti patients had anaemia than Kuwaiti patients [adjusted odds ratio (aOR), 1.34; 95% confidence interval (CI):1.16-1.56; *P* <0.001). Patients who received biologic treatment were more likely to be non-anaemic [aOR, 1.33; 95% CI:1.23-1.45; *P* <0.001). Additionally, the study demonstrated that patients with anaemia had greater odds of acquiring Disease Activity Score 28-joint count (DAS-28) ≥ 3.2 as opposed to DAS-28 < 3.2 [aOR, 0.74; 95% CI:0.61-0.90; *P* =0.002].

Conclusions: Lower haemoglobin levels in RA have been found to be an independent predictor of disease activity.

Keywords: rheumatoid arthritis, haemoglobin, biologics, DAS-28, anaemia

Introduction

Anaemia is a multifactorial, pervasive, extra-articular manifestation that is a significant burden in RA.[1,2] The most common types of anaemia in RA are chronic anaemia and iron-deficiency anaemia. A number of existing studies observed anaemia in 24.0%–70.6% of Patients with RA.[3-12] Low Hb concentrations in Patients with RA have been associated with increased mortality, extensive physical disability, and disease activity.[2,13,14] Inversely, replenishing Hb levels in anaemia was associated with improved quality of life in RA.[8] Previous studies have classified anaemia in RA according to the World Health Organization (WHO) as Hb <130 g/L in males and Hb <120 g/L in females.[3-12,16] However, a paucity of studies created a standardised low cut-off Hb value for anaemia irrespective of gender. Additionally, there are scant data regarding the prevalence, clinical and laboratory characteristics of anaemic patients with RA in Kuwait. Our aim was to stratify Patients with RA residing in Kuwait based on low and high Hb values to assess the prevalence and ascertain the association between demographics, treatment characteristics, and disease activity.

Methods

Patients with RA and Hb reports were retrospectively analysed using information collected from the KRRD. The registry design and methodology were previously delineated in detail.[17] In brief, KRRD is a prospective, national registry for adult patients diagnosed with rheumatic disease in four Kuwaiti government hospitals. Hospitals are established in different governorates to ensure ethnic diversity. Patients with RA are referred to government hospitals to undergo treatment as medicine is inexpensive for Kuwaitis and expensive for non-Kuwaitis. The study recruitment was conducted from February 2013 to February 2022.

Baseline, demographic, clinical, and laboratory data (i.e. disease activity and treatment) were obtained. Data were collected by nurses and rheumatologists who were trained to fill standard manuals or electronic forms. Informed consent was obtained from all participants. Data storage was secured through a safe digital program which connected the four hospitals. The study was approved by the Ethics Committee of the Ministry of Health in Kuwait (Letter No. VDR/JC/882 dated 10.10.2012). Informed written consent was taken from all patients.

RA was defined and classified according to American College of Rheumatology (ACR) criteria.[18] Our study defined anaemic adults as low Hb (≤110 g/L) and non-anaemic adults as high Hb (>110 g/L). We defined DAS-28 ≥ 3.2 as moderate/severe disease activity, and DAS-28 < 3.2 as low disease activity/remission; the values were calculated using a DAS calculator.[19]

The measurement of serological data was standardised across laboratories in the participating hospitals. IgM rheumatoid factor (RF) measurement was obtained quantitatively by nephelometry, and a count of >20 was positive. Anti-nuclear antibodies (ANA) were evaluated by indirect immunofluorescence using the Hep-2 cell line, and a titre > 1:40 was positive. Anti–cyclic citrullinated peptide (anti-CCP) antibodies were assessed by enzyme-linked immunosorbent assay (ELISA), and values ≥ 20 U/mL were considered positive. Although tofacitinib is a targeted synthetic disease-modifying antirheumatic drugs (DMARD), it is included here under biologics given its high efficacy in treating RA, similar to that of biologics.[20] The work has been reported in line with the STROCSS criteria.[21]

We stratified our cohort into two groups according to their Hb scores: high Hb (non-anaemic) and low Hb (anaemic). Skewed continuous variables, medians, and interquartile ranges were performed using the Mann-Whitney-Wilcoxon test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square (χ^2) test. Finally, logistic regression analysis was applied to examine the association between Hb groups and the following covariates: sex, nationality, age at RA onset, white blood cell (WBC) count, creatinine level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), DAS-28 groups (DAS-28 ≥ 3.2 and DAS-28 < 3.2), treatment (biologics and DMARDs), patient global assessment, physician global assessment, and tender and swollen joints. Statistical significance was set at P <0.05. Analysis of the dataset was performed using JAMOVI (Version 2.3.18) and SPSS (Version 28).

Results

The total number of patients visited (N_v) was 11393 and consecutive patients with RA diagnoses and Hb data (N_p) was 1584. Both N_v and N_p were included in the study. **Table 1** summarises the demographic characteristics of patients with RA stratified by Hb levels. The average age of the patients was 55.9±12.5 years and 63.4% were female. The analysis revealed significant differences in the mean age of the patients in the high (56.4±12.6) and low (54.9±12.1 years) Hb groups. The average age at RA onset in the low Hb group was significantly less (10.3 ± 6.2 years) when compared to patients with high Hb (11.3 ± 7.0 years). Among those with high Hb, the majority were Kuwaitis (51.7%),

whereas in the low Hb group, the prevalence was non-Kuwaitis (54.2%). Moreover, the analysis revealed no significant differences among the Hb groups in terms of body mass index (BMI), sex, and smoking status.

Table 1: Demographic characteristics of rheumatoid arthritis cohort stratified by Hb levels.

Characteristics, N_p (%, unless specified otherwise)	**Total (N_p =1584)**	**Hb >10 (N_p =1053)**	**Hb <10 (N_p =531)**	***P*-value**
Age, **mean ± SD, years**	55.9 ± 12.5	56.4 ± 12.6	54.9 ± 12.1	0.019[1]
Duration of RA, mean ± SD, years	11.0 ± 6.8	11.3 ± 7.0	10.3 ± 6.2	0.007[1]
Female gender	1004.0 (63.4%)	665.0 (63.2%)	339.0 (63.8%)	0.788[2]
BMI **mean ± SD, kg/m^2**	30.0 ± 12.5	30.0 ± 13.0	30.1 ± 11.1	0.849[1]
Nationality				0.027[2]
Kuwaitis	787.0 (49.7%)	544.0 (51.7%)	243.0 (45.8%)	
non-Kuwaitis	797.0 (50.3%)	509.0 (48.3%)	288.0 (54.2%)	
Smoking	112.0 (9.6%)	82.0 (10.4%)	30.0 (7.9%)	0.162[2]

Hb, hemoglobin; high Hb, Hb > 110 g/L; low Hb, Hb ≤ 110 g/L; SD, standard deviation; RA, rheumatoid arthritis; BMR, body mass index
[1]Linear Model ANOVA
[2]Pearson's Chi-squared test
Nv (total number of patients visit), Np (Total number of patients)

Table 2 outlines the association between Hb levels and the baseline medical characteristics. Notably, in the non-anaemic group, 31.9% (N_p = 265) of the patients had positive ANA, while the anaemic patients had markedly less positive ANA (24%.2, N_p = 101). The other baseline medical characteristics showed no significant differences between the two Hb groups.

Table 2: Baseline medical characteristics of rheumatoid arthritis cohort stratified by Hb levels.

Characteristics, N_p (%, unless specified otherwise)	**Total (N_p =1584)**	**Hb >10 (N_p =1053)**	**Hb <10 (N_p =531)**	***P*-value**
2ry Sjogren's	247.0 (19.3%)	175.0 (20.3%)	72.0 (17.3%)	0.218[1]
Rheumatoid Nodules	33.0 (2.5%)	20.0 (2.3%)	13.0 (3.1%)	0.408[1]
Positive RF	1118.0 (77.0%)	745.0 (77.4%)	373.0 (76.1%)	0.572[1]
Anti-CCP positive	819.0 (65.8%)	538.0 (65.4%)	281.0 (66.7%)	0.628[1]
ANA positive	366.0 (29.3%)	265.0 (31.9%)	101.0 (24.2%)	0.005[1]

Hb, hemoglobin; high Hb, Hb > 110 g/L; low Hb, Hb ≤ 110 g/L; SD, standard deviation; RF, rheumatoid factor; Anti-CCP, anti–cyclic citrullinated peptide; ANA, antinuclear antibodies; CCP, cyclic citrullinated peptide
[1]Pearson's Chi-squared test
Nv (total number of patients visit), Np (Total number of patients)

Table 3 highlights the results of the disease-modifying antirheumatic drugs (DMARDs) among the Hb groups. The low Hb group was prescribed leflunomide (LEF) (17.6% vs. 13.0%; *P* <0.001), hydroxychloroquine (HCQ) (30.4% vs. 27.5%; *P* = 0.002), and cyclophosphamide (CYC) (0.3% vs. 0.0%; *P* <0.001). In contrast, patients with high Hb levels were more commonly prescribed methotrexate (MTX) (65.2% vs. 61.9%; *P* <0.001).

Table 3: DMARDs regimen among rheumatoid arthritis cohort stratified by Hb levels.

Characteristics, N_v (%, unless specified otherwise)	**Total (N_v =11393)**	**Hb>10 (N_v =8260)**	**Hb<10 (N_v =3133)**	***P*-value**
MTX	7322.0 (64.3%)	5384.0 (65.2%)	1938.0 (61.9%)	< 0.001[1]
SSZ	1501.0 (13.2%)	1077.0 (13.0%)	424.0 (13.5%)	0.486[1]
LEF	1623.0 (14.2%)	1072.0 (13.0%)	551.0 (17.6%)	< 0.001[1]
HCQ	3222.0 (28.3%)	2270.0 (27.5%)	952.0 (30.4%)	0.002[1]
IMUR	208.0 (1.8%)	138.0 (1.7%)	70.0 (2.2%)	0.045[1]

Characteristics, Nv (%, unless specified otherwise)	Total (Nv =11393)	Hb>10 (Nv =8260)	Hb<10 (Nv =3133)	*P*-value
CYC	9.0 (0.1%)	1.0 (0.0%)	8.0 (0.3%)	< 0.001[1]

DMARDs, disease-modifying antirheumatic drugs; Hb, hemoglobin; high Hb, Hb > 110 g/L; low Hb, Hb ≤ 110 g/L; MTX, methotrexate; SSZ, sulfasalazine; LEF, leflunomide; HCQ, hydroxychloroquine; IMUR, azathioprine; CYC, cyclophosphamide

[1]Pearson's Chi-squared test

Nv (total number of patients visit), Np (Total number of patients)

Table 4 presents the results of the biological regimen between the Hb groups. A higher proportion of patients with low Hb levels were prescribed adalimumab (ADA) (7.2% vs. 5.8%; *P* = 0.005), infliximab (INF) (5.2% vs. 3.9%; *P* = 0.003), tofacitinib (TOF) (1.7% vs. 0.9%; *P* <0.001), certolizumab (CER) (2.3% vs. 1.1%; *P* <0.001), and golimumab (GOL) (1.0% vs. 0.3%; *P* <0.001). A higher proportion of patients with high Hb levels were prescribed rituximab (RIT) (12.5% vs. 9.3%; *P* <0.001), tofacitinib (TOF) (20.1% vs. 10.3%; *P* <0.001), and adalimumab (ADA) (7.5% vs. 5.8%; *P* = 0.002). Overall, a higher proportion of the high Hb group received biologics and a higher proportion of the low Hb group received DMARDs (biologics, high Hb vs. low Hb 57.2% vs. 50.0% DMARDs, low Hb 50.0% vs. high Hb 42.8%; *P* <0.001).

Table 4: Biologics regimen among rheumatoid arthritis cohort stratified by Hb levels.

Characteristics, Nv (%, unless specified otherwise)	Total (Nv =11393)	Hb>10 (Nv =8260)	Hb<10 (Nv =3133)	*P*-value
RIT	1319.0 (11.6%)	1029.0 (12.5%)	290.0 (9.3%)	< 0.001[1]
ADA	707.0 (6.2%)	480.0 (5.8%)	227.0 (7.2%)	0.005[1]
TOC	1983.0 (17.4%)	1660.0 (20.1%)	323.0 (10.3%)	< 0.001[1]
ETA	515.0 (4.5%)	355.0 (4.3%)	160.0 (5.1%)	0.063[1]
ABA	802.0 (7.0%)	619.0 (7.5%)	183.0 (5.8%)	0.002[1]
INF	486.0 (4.3%)	324.0 (3.9%)	162.0 (5.2%)	0.003[1]
TOF	124.0 (1.1%)	71.0 (0.9%)	53.0 (1.7%)	< 0.001[1]
CER	161.0 (1.4%)	88.0 (1.1%)	73.0 (2.3%)	< 0.001[1]
GOL	54.0 (0.5%)	24.0 (0.3%)	30.0 (1.0%)	< 0.001[1]
Treatment				< 0.001[1]
Biologics	6125.0 (55.3%)	4629.0 (57.2%)	1496.0 (50.0%)	
DMARDs	4959.0 (44.7%)	3465.0 (42.8%)	1494.0 (50.0%)	

Hb, hemoglobin; high Hb, Hb > 110 g/L; low Hb, Hb ≤ 110 g/L; RIT, rituximab; ADA, adalimumab; TOC, tocilizumab; ETA, etanercept; ABA, abatacept; INF, infliximab; TOF, tofacitinib; CER, certolizumab pegol; GOL, golimumab; DMARDs, disease-modifying antirheumatic drugs

[2]*Pearson's Chi-squared test*

Nv (total number of patients visit), Np (Total number of patients)

The results of laboratory tests in the cohort are summarised in **Table 5**. The analysis revealed higher values in the low Hb group for ESR, CRP, and platelet count (PLT) (*P* <0.001). Conversely, higher values were found in the high-Hb group for Hb, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total cholesterol (TC), low-density cholesterol (LDL), and uric acid (UA) (*P* <0.001).

Table 5: Findings of laboratory test in rheumatoid arthritis cohort stratified by Hb levels.

Dependent variable: Hb levels Characteristics		Total (Nv =11393)	Hb>10 (Nv =8260)	Hb<10 (Nv =3133)	*P*-value
ESR, mm/hr	Median (IQR)	23.0 (10.0 to 40.0)	22.0 (10.0 to 38.0)	26.0 (11.0 to 48.0)	<0.001[1]
CRP, mg/L	Median (IQR)	4.7 (2.0 to 8.9)	4.3 (2.0 to 8.2)	5.0 (2.0 to 9.0)	<0.001[1]
WBC, × 10^9/L	Median (IQR)	6.9 (5.4 to 8.6)	6.9 (5.4 to 8.6)	6.9 (5.4 to 8.6)	0.793[1]

Dependent variable: Hb levels Characteristics		Total (N_v =11393)	Hb>10 (N_v =8260)	Hb<10 (N_v =3133)	*P*-value
Hb, g/L	Median (IQR)	123.0 (107.0 to 134.0)	129.0 (121.0 to 138.0)	14.5 (12.2 to 101.0)	<0.001[1]
PLT, x10^9/L	Median (IQR)	264.0 (216.0 to 321.0)	261.0 (214.0 to 316.0)	273.0 (220.0 to 338.0)	<0.001[1]
Creatinine, µmol/L	Median (IQR)	59.0 (51.0 to 70.0)	60.0 (51.0 to 70.0)	59.0 (50.0 to 71.0)	0.192[1]
FBS, mmol/L	Median (IQR)	5.5 (5.0 to 6.3)	5.5 (5.0 to 6.3)	5.4 (5.0 to 6.4)	0.120[1]
AST, U/L	Median (IQR)	20.0 (17.0 to 26.0)	21.0 (17.0 to 26.0)	20.0 (16.0 to 24.0)	<0.001[1]
ALT, U/L	Median (IQR)	19.0 (14.0 to 26.0)	19.0 (15.0 to 26.0)	19.0 (14.0 to 24.0)	<0.001[1]
ALP, U/L	Median (IQR)	64.0 (50.0 to 80.0)	65.0 (51.0 to 81.0)	58.0 (45.0 to 76.8)	<0.001[1]
TC, mmol/L	Median (IQR)	4.8 (4.2 to 5.5)	4.9 (4.2 to 5.6)	4.7 (4.0 to 5.4)	<0.001[1]
LDL, mmol/L	Median (IQR)	2.8 (2.3 to 3.4)	2.9 (2.3 to 3.5)	2.7 (2.0 to 3.3)	<0.001[1]
UA, µmol/L	Median (IQR)	261.0 (206.0 to 319.0)	275.0 (227.0 to 330.0)	220.0 (193.0 to 293.0)	<0.001[1]

Hb, hemoglobin; high Hb, Hb > 110 g/L; low Hb, Hb ≤ 110 g/L; interquartile range, IQR; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cells; PLT, platelet (thrombocyte) count; FBS, fasting blood glucose; AST, aspartate aminotransferase; ALT, alanine transaminase; ALP, alkaline phosphatase; TC, total cholesterol; LDL, low-density cholesterol; UA, uric acid ; [1]Mann–Whitney–Wilcoxon test
Nv (total number of patients visit), Np (Total number of patients)

Logistic regression analysis was performed to examine clinical and demographic variables (**Table 6**). Data demonstrates a significant association between Hb levels and nationality [OR, 0.745; 95% CI: 0.643-0.862; *P* <0.001), age at RA diagnosis [OR, 0.974; 95% CI: 0.965-0.984; *P* <0.001), ESR [OR, 1.006; 95% CI: 1.003-1.009; *P* <0.001), DAS-28 levels [OR, 0.738; 95% CI: 0.607-0.896; *P* = 0.002], DMARDS and biologics treatment [OR, 1.171; 95% CI: 1.011-1.355; *P* = 0.035], patient global assessment [OR, 0.926; 95% CI: 0.880-0.975; *P* =0.004), physician global assessment [OR, 1.073; 95% CI: 1.007-1.143; *P* =0.029], tender joints [OR, 0.968; 95% CI: 0.950-0.987; *P* <0.001], and swollen joints [OR, 1.107; 95% CI: 1.075-1.139; *P* <0.001).

Table 6: Multiple logistic regression analysis of factors associated with DAS-28 in rheumatoid arthritis cohort.

Model Coefficients – Hb levels

Predictor	Estimate[+]	SE	Z	*P*-value	95% CI Odds ratio	Lower	Upper
Intercept	-0.570	0.163	-3.503	<0.001*	0.566	0.411	0.778
Gender	-0.033	0.061	-0.538	0.591	0.968	0.859	1.090
Nationality	-0.295	0.075	-3.937	<0.001*	0.745	0.643	0.862
Duration of RA, years	-0.026	0.005	-5.221	<0.001*	0.974	0.965	0.984
WBC, × 10^9/L	0.000	0.000	0.719	0.472	1.000	1.000	1.000
Creatinine, µmol/L	0.001	0.001	0.982	0.326	1.001	0.999	1.003

Model Coefficients – Hb levels

Predictor	Estimate[+]	SE	Z	*P*-value	95% CI Odds ratio	Lower	Upper
ESR, mm/hr	0.006	0.002	3.852	<0.001*	1.006	1.003	1.009
CRP, mg/L	0.003	0.006	0.474	0.635	1.003	0.991	1.015
DAS-28 < 3.2 and DAS-28 ≥ 3.2	-0.304	0.099	-3.068	0.002*	0.738	0.607	0.896
DMARDS and Biologics	0.158	0.075	2.111	0.035*	1.171	1.011	1.355
Patient Global Assessment	-0.076	0.026	-2.918	0.004*	0.926	0.880	0.975
Physician Global Assessment	0.070	0.032	2.185	0.029*	1.073	1.007	1.143
Number of Tender joints	-0.033	0.010	-3.330	<0.001*	0.968	0.950	0.987
Number of Swollen joints	0.101	0.015	6.875	<0.001*	1.107	1.075	1.139

CI; confidence interval; SE, standard error; Z, z-value; DMARD, disease-modifying antirheumatic drugs
[+] Estimate represents the log odds of low Hb (Hb ≤ 110 g/L) vs. high Hb (Hb > 110 g/L)
**P-value marked is significant*
Nv (total number of patients visit), Np (Total number of patients)

Table 7 shows the relationship between demographic and clinical parameters stratified by Hb levels using univariate and multivariate analyses. Univariate analysis revealed that sex, nationality, age at RA diagnosis, creatinine, ESR, CRP, DAS-28 levels, treatment, patient global assessment, physician global assessment, tender joints, and swollen joints were significantly associated with Hb levels. Multivariate logistic regression analysis confirmed the association of nationality, age at diagnosis, ESR, CRP, DAS-28 levels, treatment, patient global assessment, physician global assessment, tender joints, and swollen joints with Hb. **Figure 1** illustrates how the adjusted odds ratio corresponds to the demographic and clinical parameters for the dependent variable Hb. A larger number of non-Kuwaiti patients had lower Hb levels than their Kuwaiti counterparts [aOR, 1.34; 95% CI:1.16-1.56; *P* <0.001]. Patients who received biologics were more likely to have high Hb levels [aOR, 1.33; 95% CI:1.23-1.45; *P* <0.001). Additionally, patients with DAS-28 ≥ 3.2 were more likely to have had low Hb levels compared to patients with DAS-28 < 3.2 [aOR, 0.74; 95% CI:0.61-0.90; *P* =0.002).

Table 7: Univariable and multivariable logistic regression analysis of factors associated with DAS-28 in rheumatoid arthritis cohort (Version 2).

Dependent variable: Hb levels Characteristics, N_v (% unless specified otherwise)		**Hb>10**	**Hb<10**	**aOR, aP-value (univariable)**	**aOR, aP-value (multivariable)**
Gender	Male	3103 (73.7)	1106 (26.3)	0.91 (0.83-0.99, *P*=0.025) *	0.97 (0.86-1.09, *P* =0.591)
Nationality	Non-Kuwaiti's	3099 (68.0)	1456 (32.0)	1.45 (1.33-1.57, *P* <0.001) *	1.34 (1.16-1.56, *P* < 0.001) *
Age at RA onset, years	Mean ± SD	11.9 ± 6.8	10.6 ± 6.6	0.97 (0.96-0.98, *P* < 0.001) *	0.97 (0.96-0.98, *P* < 0.001)
WBC	Mean ± SD	33.3 ± 431.4	59.3 ± 1273.7	1.00 (1.00-1.00, *P* =0.166)	1.00 (1.00-1.00, *P* =0.472)
Creatinine	Mean ± SD	62.1 ± 24.6	64.1 ± 35.8	1.00 (1.00-1.00, *P* =0.001) *	1.00 (1.00-1.00, *P* =0.326)
ESR	Mean ± SD	26.4 ± 20.7	32.6 ± 26.6	1.01 (1.01-1.01, *P* < 0.001)*	1.01 (1.00-1.01, *P* < 0.001) *

Dependent variable: Hb levels Characteristics, N_v (% unless specified otherwise)		Hb>10	Hb<10	aOR, aP-value (univariable)	aOR, aP-value (multivariable)
CRP	Mean ± SD	5.8 ± 4.9	6.3 ± 5.1	1.02 (1.01-1.03, *P* < 0.001) *	1.00 (0.99-1.02, *P* =0.635)
DAS-28 Groups	DAS-28 ≥ 3.2	2212 (65.9)	1145 (34.1)		Reference
	DAS-28 < 3.2	6045 (75.3)	1988 (24.7)	0.64 (0.58-0.69, *P* < 0.001) *	0.74 (0.61-0.90, *P* =0.002) *
Treatment	Biologics	4629 (75.6)	1496 (24.4)		Reference
	DMARDS	3465 (69.9)	1494 (30.1)	1.33 (1.23-1.45, *P* <0.001) *	1.17 (1.01-1.35, *P* =0.035) *
Patient Global Assessment	Mean ± SD	1.6 ± 2.3	1.8 ± 2.4	1.03 (1.02-1.05, *P* < 0.001) *	0.93 (0.88-0.97, *P* =0.004) *
Physician Global Assessment	Mean ± SD	1.0 ± 1.7	1.2 ± 1.9	1.08 (1.06-1.11, *P* <0.001) *	1.07 (1.01-1.14, *P* =0.029) *
Tender joints	Mean ± SD	2.7 ± 5.4	3.4 ± 6.0	1.02 (1.01-1.03, *P* <0.001) *	0.97 (0.95-0.99, *P* =0.001) *
Swollen joints	Mean ± SD	0.5 ± 2.0	1.2 ± 3.0	1.11 (1.09-1.13, *P* < 0.001) *	1.11 (1.08-1.14, *P* < 0.001) *

Multivariate logistic regression
**adjusted P-value marked is significant*
Hb, hemoglobin; high Hb, Hb > 110 g/L; low Hb, Hb ≤ 110 g/L; aOR, adjusted odds ratio; aP-value, adjusted p-value; DMARD, disease-modifying antirheumatic drugs
Nv (total number of patients visit), Np (Total number of patients)

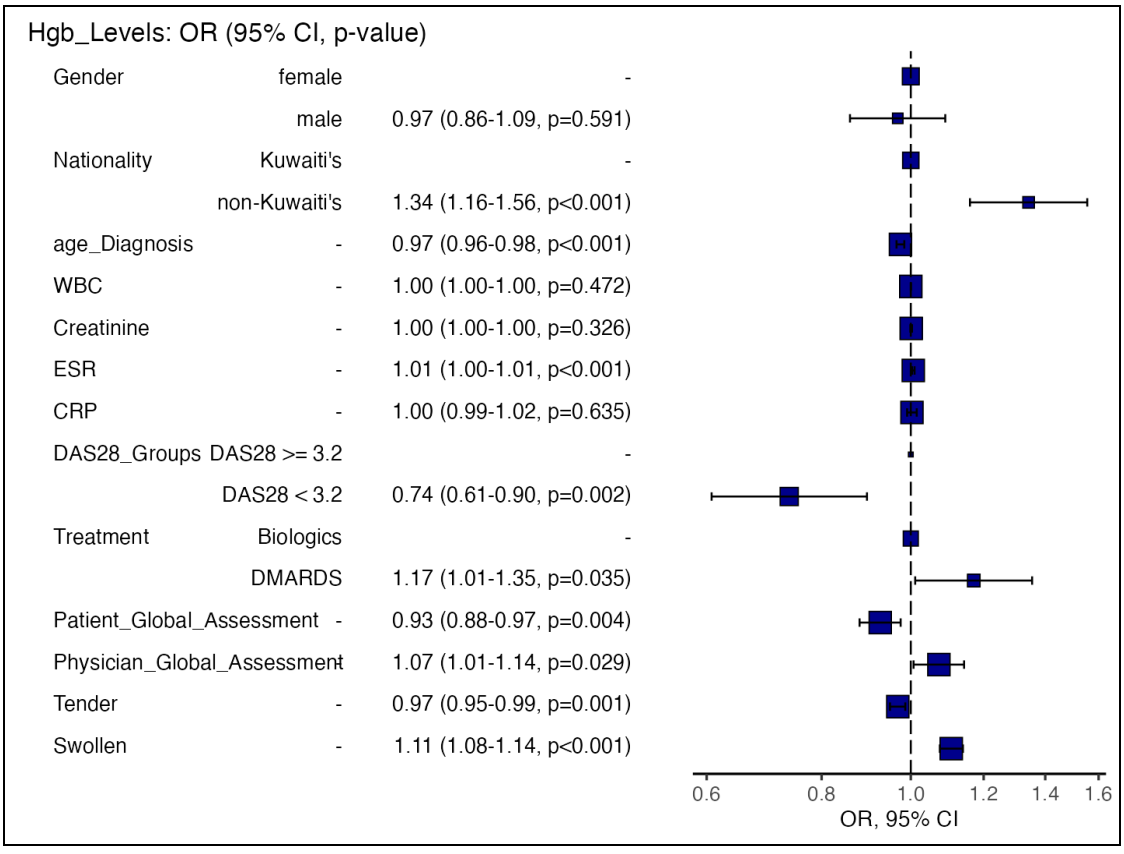

Figure 1. *Odds ratio plot of dependent and independent variables.*

Discussion

We examined the clinical impact of RA stratified by Hb levels in the KRRD cohort. The average age observed in the cohort was 55.9±12.5 years, 63.4% were females, and 50.3% were non-Kuwaiti. The median Hb level in the non-anaemic and anaemic group was 129.0 g/L and 14.5 g/L respectively. The majority of patients with positive ANA results were non-anaemic (31.9% vs. 24%.2). Regarding treatment, a higher proportion of non-anaemic patients received biologics (57.2% vs. 50.0%), in contrast to anaemic patients who were prescribed more DMARDs (42.8% vs. 50.0%). Non-Kuwaitis had 1.34 increased odds of having anaemia compared to Kuwaitis. Patients who received biologics had 1.33 increased odds of having normal Hb levels. In addition, patients with DAS-28 ≥ 3.2 had 0.74 increased odds of being anaemic in comparison to patients with DAS-28 < 3.2. Non-Kuwaiti patients may have used fewer biologics; hence, they may have a higher DAS28.[22]

Anaemic syndrome has been previously reported as a marker of high activity and severity in Patients with RA[3,23] **Table 8** compares our KRRD cohort with other international studies to evaluate the severity of the disease.[6-12] All studies included lower Hb level thresholds for females. The AMU study had the lowest cut-off Hb values (<110 g/L in females and <120 g/L in males).[11] Most studies adhered to the Hb concentrations proposed by the WHO.[6,8-10,12] Our study is the sole study to discount sex and use a generalised low cut-off score. International data have reported that 24.0% to 70.6% of patients with RA have anaemia. **[Table 8]** The prevalence of anaemia in our study was 27.5%, approximately fourfold lower than that reported by Agrawal et al. (70.6%), Goyal et al. (67.8%), and Ganna (64.0%).[7,9,10] This was akin to SCQM's Swiss study (24.0%) and the Moroccan QUEST-RA study (28.8%).[6,8] All the studies were in consensus that anaemic patients had higher DAS-28 scores and a larger number of tender and swollen joints. These studies reported a negative correlation between Hb concentration and DAS-28 and the number of swollen/tender joints. Similarly, in our study, more anaemics had a DAS-28 ≥ 3.2 than non-anaemics (36.5% vs. 26.8). Furthermore, patients with anaemia had a higher prevalence of swollen (1.2 ± 3.0 vs. 0.5 ± 2.0) and tender joints (3.4 ± 6.0 vs. 2.7 ± 5.4). Notably, our study had lower averages for swollen and tender joints than other international studies.[7,9-12]

Table 8: Comparison of KRDD and other international studies.

Study, Country	**Study period (year)**	***N* RA**	***n Anaemia (%)***	**Hb level cut-off for anaemia (g/L)**	**DAS-28 anaemic vs. non-anaemic (unless specified otherwise)**	**Swollen joint anaemic vs. non-anaemic**	**Tender joint anaemic vs. non-anaemic**
SCQM, Switzerland[6]	1996-2007	4377	1054 (24.0%)	F < 120 g/L M < 130 g/L	**DAS-28 mean ± SD =** 5.2 ± 1.5 vs. 4.2 ± 1.4	-	-
Agrawal, S., et al, India[7]	2003	214	151 (70.6%)	F ≤ 110 g/L M ≤ 120 g/L	**DAS-28 mean ± SD** = 5.19 **±** 1.50 vs. 3.82 ± 1.36	**mean ± SD** = 8.81 ± 8.08 vs. 3.82 ± 5.77	**mean ± SD** = 5.37 ± 6.32 vs. 2.23 ± 4.27
Moroccan QUEST-RA, Morocco[8]	2008-2010	1032	297 (28.8%)	F < 120 g/L M < 130 g/L	**DAS-28 mean ± SD** = 5.45 ± 1.55 vs. 4.7 ± 1.69	-	-
Ganna, S., Ukraine[9]	2014	89	57 (64.0%)	F < 120 g/L	**DAS-28 mean ± SD** = 5.2 ± 1.3 vs. 2.8 ± 1.1	**mean ± SD** = 28.67 ± 9.01 vs. 16.53 ± 8.27	**mean ± SD** = 31.42 ± 10.07 vs. 18.52 ± 11.28
Goyal, L., et al, India[10]	2012-2013	59	40 (67.80%)	F < 120 g/L M < 130 g/L	**DAS-28 3.2-5.1** = 20.0% vs. 80.0% **DAS-28 >5.1** = 92.0% vs. 8..0%	**mean ± SD** = 9.17 ± 3.82 vs. 2.35 vs. 0.93	**mean ± SD** = 12.98 ± 4.21 vs. 5.82 vs. 2.10
AMU, China[11]	2015-2018	890	418 (47.05)	F < 110 g/L M < 120 g/L	**DAS28 mean ± SD** = 5.80 ± 1.09 vs. 4.80 ± 1.32	**median (IQR)** = 8 (4–12) vs. 5 (2–10)	**median (IQR)** = 12 (7–20) vs. 8 (4–15)

RIMS, India[12]	2018 - 2020	236	139 (58.9%)	F < 120 g/L M < 130 g/L	**DAS28 mean ± SD** = 4.71 ± 1.25 vs. 1.14 ± 1.15	**mean ± SD** = 6.17 ± 4.27 vs. 2.91 ± 2.52	**mean ± SD** = 3.71 ± 3.21 vs. 0.123 ± 0.1
KRDD, Kuwait	2013-2022	N_v =11393 N_p=1584	N_v = 3133 (27.5%)	M and F ≤ 110 g/L	***Hb<10** = 26.8% vs. 73.2% ***Hb>10** = 36.5% vs. 63.5%	**mean ± SD** = 1.2 ± 3.0 vs. 0.5 ± 2.0	**mean ± SD** = 3.4 ± 6.0 vs. 2.7 ± 5.4

***compares DAS-28 ≥ 3.2 vs. DAS-28 < 3.2*
RA, rheumatoid arthritis; SCQM, Swiss clinical quality management; QUEST-RA, Quantitative Standard Monitoring Patients with RA; AMU, Anhui Medical University; RIMS, Regional Institute of Medical Sciences; M, male; F, female; IQR, interquartile range
Nv (total number of patients visit), Np (Total number of patients)

Patients with anaemia tend to have elevated inflammatory acute-phase reactants compared to their non-anaemic counterparts. A previous analysis conducted by Wolfe et al. on 2120 patients with RA demonstrated CRP and ESR to be predictors of anaemia.[24] In our study, anaemic patients were associated with 1.01 increased odds of elevated ESR, but CRP was not significant. The treatment of disease activity and inflammation is believed to improve Hb levels.[25] However, long-term DMARDs therapy is associated with abnormal absorption of iron and vitamin B12 as a consequence of gastrointestinal mucosal damage or ulcers.[11,26] Emerging data reports tumour necrosis factor (TNF-α) is significantly higher in anaemic Patients with RA.[27] Correspondingly, biologics, such as tocilizumab and adalimumab, have been associated with significant improvements in anaemia.[28,29] We did not study Hb concentration prior to drug administration; thus, we could not ascertain any improvements due to biologics. However, there is an association between biologics and normal Hb levels in patients.

As this was a retrospective study, the study could introduce bias through confounding variables which were unaccounted for, such as history of nonsteroidal anti-inflammatory and glucocorticoid drug use. Moreover, the aetiology and haematological features of anaemia were not identified. In our study the stratification was done according to haemoglobin levels and not as per the definition of anaemia. Furthermore, we did not delineate the changes in Hb concentration before and after treatment. Further studies are required to overcome these limitations.

Conclusions

The results establish an interrelation between inflammation and anaemia, expressed by the significant association between low Hb levels, higher DAS-28 scores and ESR. Taken together, results suggest that low Hb levels is a predictor of worse outcomes in patients with RA.

Conflict of interest disclosure:

No conflict of interest exists for any author on this manuscript.

Sources of funding:

No funding availed.

References

1. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007 Oct;21(5):885-906.

2. Han C, Rahman MU, Doyle MK, Bathon JM, Smolen J, Kavanaugh A, et al. Association of anemia and physical disability among patients with rheumatoid arthritis. J Rheumatol 2007 Nov;34(11):2177-2182.

3. Furst DE, Chang H, Greenberg JD, Ranganath VK, Reed G, Ozturk ZE, et al. Prevalence of low hemoglobin levels and associations with other disease parameters in rheumatoid arthritis patients: evidence from the CORRONA registry. Clin Exp Rheumatol 2009;27(4):560-566.

4. Wilson A, Yu HT, Goodnough LT, Nissenson AR. Prevalence and outcomes of anemia in rheumatoid arthritis: a systematic review of the literature. Am J Med 2004 Apr;116(Suppl 7A):50S-57S.

5. Al-Ghamdi A, Attar SM. Extra-articular manifestations of rheumatoid arthritis: a hospital-based study. Ann Saudi Med 2009;29(3):189-193.

6. Möller B, Scherer A, Förger F, Villiger PM, Finckh A; Swiss Clinical Quality Management Program for Rheumatic Diseases. Anaemia may add information to standardised disease activity assessment to predict radiographic damage in rheumatoid arthritis: a prospective cohort study. Ann Rheum Dis 2014 Apr;73(4):691-696.

7. Agrawal S, Misra R, Aggarwal A. Anemia in rheumatoid arthritis: high prevalence of iron-deficiency anemia in Indian patients. Rheumatol Int 2006 Oct;26(12):1091-1095.

8. Hajar TL, Rostom S, Hari A, Lahlou R, Bahiri R. etal. Prevalence of Anemia and its Association with Parameters of Rheumatoid Arthritis Patients: A Study from the Moroccan Quest - RA Data. J Palliat Care Med 2015;5:221. .

9. Smyrnova G. Relação entre o nível de hemoglobina e a atividade da doença em pacientes com artrite reumatoide. (The relationship between hemoglobin level and disease activity in patients with rheumatoid arthritis). Rev Bras Reumatol 2014;54(6):437-440.

10. Goyal L, Shah PJ, Yadav RN, Saigal R, Agarwal A, Banerjee S. Anaemia in Newly Diagnosed Patients of Rheumatoid Arthritis and its Correlation with Disease Activity. J Assoc Physicians India 2018 May;66(5):26-29.

11. Chen YF, Xu SQ, Xu YC, Li WJ, Chen KM, Cai J, et al. Inflammatory anemia may be an indicator for predicting disease activity and structural damage in Chinese patients with rheumatoid arthritis. Clin Rheumatol 2020 Jun;39(6):1737-1745.

12. Shanti Devi T, et al. Prevalence of anemia in rheumatoid arthritis and its correlation with disease activity. IOSR J Dent Med Sci 2020;19(12):27-32.

13. Furst DE, Chang H, Greenberg JD, Ranganath VK, Reed G, Ozturk ZE, et al. Prevalence of low hemoglobin levels and associations with other disease parameters in rheumatoid arthritis patients: evidence from the CORRONA registry. Clin Exp Rheumatol 2009;27(4):560-566.

14. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005 Mar;352(10):1011-1023.

15. Kaltwasser JP, Kessler U, Gottschalk R, Stucki G, Möller B. Effect of recombinant human erythropoietin and intravenous iron on anemia and disease activity in rheumatoid arthritis. J Rheumatol 2001 Nov;28(11):2430-2436.

16. Haemoglobin WH. Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Vitamin and Mineral Nutrition Information System. World Health Organization, Geneva, 2011; WHO/NMH/NHD/MNM/11.1. http://www.who.int/vmnis/indicators/haemoglobin.pdf

17. Al-HerzA. Al-AwadhiA., SalehK., Al-KandariW., HasanE., GhanemA., AbutibanF., AleniziA., HussainM., AliY., KhadrawyA., FazalA., MokaddemK., AftabB., HaiderN., ZamanA., MazloumG., BartellaY., HamedS., & Al-SaberA. A Comparison of Rheumatoid Arthritis Patients in Kuwait with Other Populations: Results from the KRRD Registry. J Adv Med Med Res 2016;14(9):1-11.

18. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010 Sep;62(9):2569-2581.

19. Jensen Hansen IM, Asmussen Andreasen R, van Bui Hansen MN, Emamifar A. The Reliability of Disease Activity Score in 28 Joints-C-Reactive Protein Might Be Overestimated in a Subgroup of Rheumatoid Arthritis Patients, When the Score Is Solely Based on Subjective Parameters: A Cross-sectional, Exploratory Study. J Clin Rheumatol 2017 Mar;23(2):102-106.

20. Al-Herz A, Saleh K, Al-Awadhi A, Al-Kandari W, Hasan E, Ghanem A, et al; Kuwait Registry for Rheumatic Diseases (KRRD). Accessibility to biologics and its impact on disease activity and quality of life in patients with rheumatoid arthritis in Kuwait. Clin Rheumatol 2021 May;40(5):1759-1765. .

21. Agha R, Abdall-Razak A, Crossley E, Dowlut N, Iosifidis C, Mathew G; STROCSS Group. STROCSS 2019 Guideline: Strengthening the reporting of cohort studies in surgery. Int J Surg 2019 Dec;72:156-165.

22. Al-Herz A, Saleh K, Al-Awadhi A, Al-Kandari W, Hasan E, Ghanem A, et al; Kuwait Registry for Rheumatic Diseases (KRRD). Accessibility to biologics and its impact on disease activity and quality of life in patients with rheumatoid arthritis in Kuwait. Clin Rheumatol 2021 May;40(5):1759-1765. .

23. Borah DJ, Iqbal F. Anemia in Recent Onset Rheumatoid Arthritis. JK Science. 2007;9(3):120-122.

24. Wolfe F, Michaud K. Anemia and renal function in patients with rheumatoid arthritis. J Rheumatol 2006 Aug;33(8):1516-1522.

25. Mahmoud AA, Ismail MA. Anemia, Iron status and calcium-phosphorus levels in rheumatoid arthritis pations. Biofactors 2012;10(7):110-114.

26. Moreland LW, Curtis JR. Systemic nonarticular manifestations of rheumatoid arthritis: focus on inflammatory mechanisms. Semin Arthritis Rheum 2009 Oct;39(2):132-143.

27. Kullich W, Niksic F, Burmucic K, Pöllmann G, Klein G. [Effects of the chemokine MIP-1alpha on anemia and inflammation in rheumatoid arthritis]. Z Rheumatol 2002 Oct;61(5):568-576.

28. Hashimoto M, Fujii T, Hamaguchi M, Furu M, Ito H, Terao C, et al. Increase of hemoglobin levels by anti-IL-6 receptor antibody (tocilizumab) in rheumatoid arthritis. PLoS One 2014 May;9(5):e98202.

29. Sakthiswary R, Syahrul Sazliyana S, Mohd Shahrir MS, Shahril NS, Hussein H. Beyond the joints in rheumatoid arthritis: Effects of adalimumab on hematologic and lipid indices. EXCLI J 2012 Apr;11(1):142-149.